Appendix E
Toxicity Profile for Polychlorinated Biphenyls

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Polychlorinated biphenyls (PCBs) are a group of synthetic organic chemicals consisting of 209 individual compounds, or congeners. A congener may have between 1 and 10 chlorine atoms located at various positions on the PCB molecule. Monochlorobiphenyls have one chlorine atom per molecule; dichlorobiphenyls have two chlorine atoms per molecule. This pattern progresses up through decachlorobiphenyls with ten chlorine atoms per molecule.

There are no known natural sources of PCBs. Before 1977, PCBs entered the water, air and soil during their manufacture and use. PCBs also entered the environment as a result of spills, leaks or fires in capacitors or transformers containing PCBs. PCBs can enter the environment today through poorly maintained hazardous waste sites, illegal or improper dumping of wastes, or disposal of PCB-containing consumer products into municipal landfills not designed to handle hazardous waste. Municipal and industrial incinerators that burn organic wastes can also release PCBs into the environment (ATSDR 1998).

PCBs were used extensively in the United States from the 1930s through 1977, when the manufacture of PCBs was banned. PCBs mixtures have several chemical and physical properties, which made them useful in a variety of industrial applications including resistance to acids and bases as well as oxidation and reduction; compatibility with organic materials; and thermal stability and nonflammability. The major uses of PCBs were as dielectric fluids in capacitors and transformers; as additives in paint, plastics, newspaper print, and dyes; as extenders in pesticides; and as heat transfer and hydraulic fluids (Kimbrough, et al. 1999).

People may be exposed to PCBs from the workplace and from the environment. Exposures occur through contact with air, water, soil, breast milk, and food. Exposure can also occur in utero. The primary pathway of exposure to PCBs in the Great Lakes region is through the food pathway, particularly through the consumption of fish (ATSDR 1998). Susceptible populations include certain ethnic groups, sport anglers, the elderly, pregnant women, children, fetuses and nursing infants.

Summary of Health Effects Associated with PCBs - Human Health Studies

The Agency for Toxic Substances and Disease Registry (ATSDR) and the U.S. Environmental Protection Agency (EPA) have jointly developed a technical paper, Public Health Implications of Polychlorinated Biphenyls (PCBs) Exposure. Human health studies discussed in this paper indicate that exposure to PCBs have been linked to the following health effects:

- Reproductive function in women
- Neurobehavioral and development deficits in newborns and school-age children from in utero exposure
- Liver disease, immune function impacts, and thyroid effects
- Increased cancer risks

Several studies have demonstrated a correlation between fish consumption by mothers and developmental disorders and cognitive deficits in children. In the first of these studies, conducted by Jacobson (Jacobson, et al. 1985, 1990a, 1990b, 1996), statistically significant decreases in gestational age, birth weight, and head circumference were observed and continued to be evident 5 to 7 months after birth. Neurobehavioral deficits were observed including depressed responsiveness, impaired visual recognition, and poor short-term memory at 7 months of age, which continued to be present at 4 years of age. While recognized limitations exist in these studies, including the pooling of blood samples, which is no longer a recognized technique, more recent studies have provided confirmatory evidence of the relationship between PCB exposure and developmental effects.

In a study of prenatal exposure and neonatal behavioral assessment scale (NBAS) performance, cord blood PCBs, DDE, HCB, Mirex, lead, and hair mercury levels were determined for 152 women who reported never consuming Lake Ontario fish and 141 women who reported consuming at least 40 PCB-equivalent pounds of Lake Ontario Fish over a lifetime. PCBs were related to impaired performance on those NBAS clusters associated with fish consumption, namely, Habituation and Autonomic clusters. Results revealed significant linear relationships between the most heavily chlorinated PCBs and performance impairments 25 to 48 hours after birth. Higher prenatal PCB exposure was also associated with nonspecific performance impairment (Stewart, et al. 2000). PCBs of lighter chlorination were unrelated to NBAS performance.

Studies in Japan and Taiwan of PCB exposure from consumption of contaminated rice oil have contributed to the evidence of an association between PCBs and neurobehavioral effects. The illnesses were originally referred to as Yusho disease in Japan and Yu-Cheng disease in Taiwan. In earlier studies (Bandiera, et al. 1984; Kunita, et al.; Masuda and Yoshimura 1984; Ryan, et al. 1990; ATSDR 1993) co-contaminants in the rice oil, particularly chlorinated dibenzofurans (CDFs), were considered to be the primary causal agent. Recent studies, however, involving a re-examination of previous studies and newer results from a study of children born later to exposed mothers have demonstrated developmental delays associated with maternal exposure to PCBs and CDFs (Guo, et al. 1995; Chao, et al. 1997).

A study of Inuit women from Hudson Bay indicated an association between levels of PCBs and dichlorodiphenylethene (DDE) in breast milk and a statistically significant

reduction in male birth length (Dewailley, et al. 1993a). No significant differences were observed between male and female newborns for birth weight, head circumference, or thyroid-stimulating hormone.

A study of 338 infants of mothers occupationally exposed to PCBs during the manufacture of capacitors indicated a decrease in gestational age (6.6 days) and a reduction in birth weight (153 grams) at birth in infants of mothers directly exposed to PCBs (Taylor, et al. 1984). A follow-up study of 405 women in this population demonstrated that serum total PCB levels in women with direct exposure to PCBs were more than four-fold higher than for women in indirect-exposure jobs. A decrease in birth weight and gestational age was found for the infants of these women (Taylor, et al. 1989).

Immune system effects on persons exposed to PCBs have been reported in several studies. A significant negative correlation between weekly consumption of fish containing PCBs from the Baltic Sea and white cell count was reported (Svensson 1994). Immune system effects were reported in Inuit infants who were believed to have received elevated levels of PCBs and dioxins from their mother's breast milk. Effects included a decline in the ratio of the CD4+ (helper) to CD8+ (cytotoxic) T-cells at ages 6 and 12 months (Dewailley, et al. 1993). Infants examined from birth to 18 months who were exposed to PCBs / dioxins in the Netherlands exhibited lower monocyte and granulocyte counts and increases in the total number of T-cells and the number of cytotoxic T-cells (Weisglas-Kuperous, et al. 1995). An increase in serum PCB levels was associated with a decrease in natural killer cells (Hagamar, et al. 1995).

Effects on the thyroid have been reported in a study of the Dutch population. Higher CDD, CDF, and PCB levels in human milk correlated significantly with lower plasma levels of maternal total triiodothyronine and total thyroxine and higher plasma levels of thyroid-stimulating hormone in infants during the second and third month after birth (ATSDR 1998).

Occupational studies show some increases in cancer mortality in workers exposed to PCBs. Significant excesses of cancer mortality were found for liver, gall bladder, and biliary tract cancer (Brown 1987), however, co-exposure to other chemicals in the workplace limits the strength of the association to PCBs. Mortality from gastrointestinal tract cancer in males and hematologic neoplasms in females was reported for capacitor workers in Italy (Bertazzi, et al. 1987). Limitations in this study include a small number of cases, short exposure period, and lack of pattern or trend when data were analyzed by duration of exposure. The results of these studies have been evaluated and are considered inconclusive by the ATSDR (1996).

Evidence of an association between exposure to PCBs by capacitor workers and mortality from malignant melanoma was reported (Sinks, et al. 1992). The workers were also exposed to various solvents. More deaths were observed than expected for malignant melanoma (8 observed versus 2 expected) and cancer of the brain and

central nervous system (5 observed versus 2.8 expected). Limitations include a small number of cases, insufficient monitoring data, unknown contribution of exposure to solvents, and possible bias due to the healthy worker effect. The results of this study have been evaluated and are considered inconclusive by ATSDR.

A recent study of male and female capacitor workers reported mortality from all cancers was significantly below expected for hourly male workers and comparable to expected for female workers (Kimbrough, et al. 1999). Limitations with this study include:

- Exposed and unexposed workers were included as one group diluting any potential cancer findings
- 76 percent of the workers never had exposure to PCBs
- Only 4 percent of the workers had any PCB blood data and only 2 percent worked in jobs with high exposure to PCBs
- 79 percent of the workers who did die of cancer had PCB exposures less than 1 year

ATSDR has stated it is untenable to dismiss concerns for carcinogenicity of PCBs. In 1999, the ATSDR convened an Expert Panel Review of the Toxicological Profile for PCBs. The panel concurred that the Kimbrough study of General Electric capacitor workers could not be used to dismiss the carcinogenic potential of PCBs (Bove, et al. 1999).

For reasons such as those above, EPA also concludes that the limitations of the Kimbrough study prevent conclusions to be drawn regarding the carcinogenicity of PCBs. While all human studies have limitations and confounders, controlled animal studies, such as a long term bioassay conducted by General Electric (Mayes 1998) provide conclusive evidence that PCBs, including the lower chlorinated forms (i.e., Aroclor 1016 and 1242) cause cancer. For this reason, the International Agency for Research on Cancer (IARC) and EPA have concluded that the PCBs are probable human carcinogens. These conclusions are independently consistent with the National Toxicology Program's eight Report on Carcinogens, which lists PCBs as "reasonably anticipated to be human carcinogens."

A recent study demonstrated a strong dose-response relationship between total lipid-corrected serum PCB concentrations and the risk of non-Hodgkin lymphoma (Rothman, et al. 1997). These findings are consistent with another study where residues of PCBs in adipose tissue of non-Hodgkin's lymphoma patients were higher than those of control patients (Hardell, et al. 1996). In studies of capacitor workers, significantly increased risks were reported for lymphatic / haematological malignant (LHM) diseases among female capacitor workers but non-significant increases were found for male workers (Bertazzi, et al. 1987). Two other studies found no evidence of increase in LHM among workers (Brown 1987; Sinks, et al. 1992).

Animal Studies

Four PCB mixtures - Aroclor 1016, 1242, 1254, and 1260 have induced liver tumors when fed to female rats. Aroclor 1260 also induced liver tumors in male rats (Mayes, et al. 1998). Thyroid gland tumors were induced in male rats in the same studies. Lifetime dietary exposure to PCB mixtures with 60 percent chlorine induced liver tumors in three rat strains (Kimbrough, et al. 1975; Schaeffer, et al. 1984; Norback and Weltman 1985; Moore, et al. 1994). The Mayes study provided strong evidence that all PCB mixtures can cause cancer. Based on animal studies, IARC has concluded that PCBs are probable human carcinogens.

Other health effects observed in animals exposed to PCB include neurotoxicity, thyroid gland effects, immune system effects, and reproductive effects. Neurobehavioral effects in the offspring of monkeys have been associated with Aroclors 1248, 1242, and 1016 (Bowman, et al. 1978; Levin, et al. 1988; Schantz, et al. 1989; and Rice 1999). Rats exposed to PCBs exhibited thyroid gland enlargement, reduced follicular size, follicular cell hyperplasia, abnormally shaped lysosomes in the follicular cells, and decreased levels of adrenal cortex hormones which were dose-related (Byrne, et al. 1987, 1988).

Rats treated with Aroclor 1254 had reduced thymus weights and reduced natural killer cell activities (Smialowicz, et al. 1989). Monkeys exposed to Aroclor 1254 had a significant decrease in IgM and IgG levels in primary response to challenge with sheep red cells (Tryphonas, et al. 1989). Effects on the immune system, demonstrated in several species, form the basis of the EPA reference dose (RfD) for Aroclor 1254 (ATSDR 1998).

Monkeys exposed in utero and through breast milk to PCBs exhibited lower birth weights, hyperpigmentation, and significantly impaired neurobehavioral test results (Schantz 1989, 1991).

Health Studies in the Great Lakes Basin

Research indicates that the primary pathway of exposure to PCBs in the Great Lakes region is from fish consumption. Recent evidence indicates an association between PCB exposures through fish consumption and reproductive and developmental effects. Newborns of mothers in the high fish consumption category exhibited a greater number of abnormal reflexes, less mature autonomic responses and less attention to visual and auditory stimuli (Lonky, et al. 1996).

The Lake Michigan Maternal Infant Cohort study was the first epidemiologic investigation to demonstrate an association between the self-reported amounts of Lake Michigan fish eaten by pregnant women and behavioral deficits in their newborns. The 242 infants born to mothers who had eaten the greatest amount of contaminated fish during pregnancy had (1) more abnormally weak reflexes; (2) greater motor immaturity and more startle responses; and (3) less responsiveness to

stimulation (ATSDR 1998). A follow-up examination of 212 children indicated that the neurodevelopmental deficits found during infancy and early childhood still persisted at age 11 years (Jacobsen and Jacobsen 1996).

In a study of nervous system dysfunction in adults exposed to PCBs and other persistent toxic substances, motor slowing and attention difficulties were directly related to the frequency of consumption of St. Lawrence Lakes fish (Mergler 1997, 1998).

In an ongoing study of Native Americans in Minnesota, Wisconsin, and Michigan preliminary results indicated elevated serum PCB levels were correlated with self-reported diabetes and liver disease (Dellinger, et al. 1997; Tarvis, et al. 1997; Gerstenberger, et al. 1997). The average annual fish consumption rate was 23 grams per day.

In a study of the PCB congener profile in the serum of humans consuming Great Lakes fish, an established cohort of persons with robust exposure to contaminants in recreationally caught Great Lakes fish were shown to have significant quantities of serum PCBs still present 15 years after enrollment in the study. The current levels of PCBs in this group were far above those found in enrollees of more recent fish eater studies. Identification of the PCB profile in fish eaters and non-fish eaters revealed the presence of several congeners that have the potential to affect biologic or health outcomes. Investigators are currently in the process of evaluating neuropsychologic function and thyroid function in the Lake Michigan fish eaters for which PCB congener profiles were established (Humphrey, et al. 2000).

The Kalamazoo River Angler Survey (MDCH 2000b) included a second phase that included a health survey and biological testing. In this second phase, individual self-reported medical information and fish consumption patterns was obtained and chemical analyses for PCBs, DDE, and mercury was performed on blood samples of 151 out of the original 938 survey participants. The study attempted to analyze for possible associations between chemical residue levels and self-reported health problems for fish eaters and compared chemical residue data from this study cohort to other fish eating populations previously studied.

The study reported that "medical problems reported as subjective symptoms (upset stomach, nausea, headache, or dizziness) were not measurable or quantifiable in an objective way. Statistically significant associations were not found between contaminant residues levels and self-reported medical problems. However, those anglers who considered themselves to be in good health appeared to be less likely to have blood PCB levels exceed median values for the aggregate group than anglers who considered themselves to be in fair / poor health."

Significantly higher levels of PCBs were found in fish eaters compared with non-fish eaters. The geometric mean for fish eaters was 2.1 ppb PCBs in blood and for non-fish eaters was 1.11 ppb PCBs in blood. Increasing residue levels for PCBs suggested a

good correlation with age reflecting the persistence of these compounds in human tissues and possible higher past exposures. In contrast to previous studies of sport anglers, the Kalamazoo River Survey appears to indicate lower exposure to PCBs. Lake Michigan open water fish eaters were first evaluated in 1979-1980 and reevaluated in 1989 (Humphrey 1988; Hovinga, et al. 1992). The Lake Michigan fish eaters consumed an annual average of 32 pounds (64 meals per year) of sport-caught fish, whereas the Kalamazoo anglers consumed an annual average of 9 pounds (18 meals per year) of sport-caught fish. The Kalamazoo fish eaters more closely resembled the non-fish eaters in the Lake Michigan study.

In a comparison of Kalamazoo anglers with a survey of anglers on Wisconsin inland lakes and rivers (Fiore 1989), the following was observed: (1) Kalamazoo anglers ate on average less fish than the Wisconsin anglers but had higher PCB levels; (2) 59 of the Wisconsin anglers had no detectable PCBs while only 10 Kalamazoo River anglers were nondetectable; (3) the upper range of serum PCBs (73 ppb) reported in Kalamazoo was more than two and one-half times the upper range seen in Wisconsin (27.1 ppb).

Limitations of Phase II of the Kalamazoo River Angler Survey include: (1) selection bias in that the study group was self-selected; (2) fish consumption within the past 12 months was used as the exposure variable, rather than historic consumption; (3) response bias due to participants knowing the purpose of the study; and (4) biases associated with self-reporting health effects.

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